

# Prescribing Warfarin Appropriately to Meet Patient Safety Goals

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The anticoagulant warfarin is increasingly used in a variety of disorders associated with risk of thromboembolism. The drug is undoubtedly effective but is linked to numerous nutrient, disease, and drug interactions; safe use of warfarin therefore necessitates close patient monitoring, using the international normalized ratio. The predominant adverse effect is bleeding, and individuals respond to warfarin in different ways. Both high and subtherapeutic international normalized ratios warrant attention, whereas a high international normalized ratio, with or without bleeding, mandates prompt patient evaluation. The

2008 National Patient Safety Goals require medical institutions to develop processes to ensure the safe use and monitoring of anticoagulant use. Last August, the US Food and Drug Administration revised the prescribing information for warfarin to include genetic testing before initiating therapy, although this is still not covered by most health plans. [AHDB. 2008;1(6):26-32.]

Warfarin, which has been in use for more than 50 years, has received considerable attention because of its common use for several indications and the link to adverse events, some life-threatening, which require close monitoring of the international normalized ratio (INR). The drug is undoubtedly effective, but has a narrow therapeutic index. In a 12-month observational study of 25 nursing homes, one sixth of the approximate 3000 residents received warfarin, which resulted in 720 adverse events<sup>1</sup>; many of the events were preventable, raising safety concerns.<sup>1</sup>

Warfarin use is on the increase and with it a higher prevalence of bleeding events, which prompted the addition of a “black box” warning by the US Food and

Drug Administration (FDA).<sup>2</sup> The Joint Commission National Patient Safety Goals requirements for 2008 have stated in goal 3E, “the need to reduce the likelihood of patient harm associated with the use of anticoagulant therapy”<sup>3</sup>; thus hospitals and long-term care institutions have to develop performance improvement processes to ensure the safe use of warfarin.

## Pharmacokinetics and Pharmacodynamics

Warfarin is a racemic mixture of 2 isomers, R and S forms, in equal proportion.<sup>4</sup> Anticoagulants of the coumarin type, such as warfarin, act by blocking the conversion of inactive vitamin K to the reduced state, a requirement to form procoagulant factors II, VII, IX, and X. Besides vitamin K-dependent clotting factors, warfarin inhibits endogenous anticoagulant proteins C and S.<sup>5</sup> Half-lives of clotting factors vary considerably, the shortest being factor VII and the longest being factor II.

Warfarin has a narrow therapeutic index, with unpredictable and variable pharmacokinetics influenced by genetic, disease, and environmental factors. It is 99% protein-bound; variations in albumin level, particularly declines after illness, result in lower dose requirements. An exaggerated response in older patients may be caused by reduced clearance of the drug.<sup>4</sup> Warfarin has both anticoagulant and antithrombotic effects. Anticoagulant activity results from clear-

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ance of clotting factors, the earliest being factor VII (with shortest half-life of 6 hours) manifested in the INR within 24 to 36 hours; antithrombotic effects occur by 5 days of therapy, due to clearance of factor II (prothrombin, half-life 50+ hours) (Table 1).<sup>4,5</sup>

Bleeding is the well-recognized side effect, with consequences relating to extent of bleed and location. The likelihood of bleeding increases with intensity of anticoagulation. A less-recognized and rare but bothersome side effect is skin necrosis, seen within a few days of therapy. Necrosis occurs in the extremities, penis, or the breasts, and results from a rapid drop in protein C (or with inherited protein C or S deficiency), causing thrombosis of the microvasculature. Rarely encountered is a painful blue discoloration of the toes (purple toe syndrome) attributed to cholesterol emboli from plaques.

For decades, anticoagulant effects of warfarin were monitored by measuring prothrombin time (PT) to assess decline in activity of clotting factors II, VII, and X. However, the test was fraught with variations in thromboplastin sensitivities, leading to dosing irregularities and confusion in prescribing warfarin.

The introduction of INR as the guide for anticoagulation allows comparison of test results from different laboratories and standardized therapeutic ranges. INR targets are individualized to risk and indication for anticoagulation. However, INR lacks validity during the induction and withdrawal phases of warfarin therapy.<sup>4,5</sup> The use of PT is no longer considered safe or acceptable.

### Appropriate Dosing

The typical initial dose of warfarin is 5 mg, followed by a maintenance dose of 2 to 5 mg/day. In the elderly, it is important to use a low loading dose; the target INR is often achieved with a smaller maintenance dose.<sup>6</sup> Prescribers need to resist starting with higher loading doses of warfarin because not all coagulation factors inhibited by warfarin decline at the same time; factor II, with the longest half-life, drops last. Also, during induction, proteins C and S, both with anticoagulant properties, get depressed earlier, resulting in a potentially hypercoagulable situation for a brief period. Hence, heparin is added when immediate anticoagulation is required and the INR is not at therapeutic levels.<sup>6,7</sup> Use of higher initial doses of warfarin can lead to bleeding and clotting complications.

Typical maintenance is best managed with 1 generic or brand-name preparation; switching from one to the other may lead to variations in bioavailability,

## KEY POINTS

- ▲ Although warfarin has significant benefits for patients at risk for thromboembolism, its use is associated with adverse events linked to drug, nutrient, and disease interactions.
- ▲ The most dangerous side effect of warfarin is bleeding, which is linked to a high INR, initial dose, age, and certain comorbidities. Monitoring the INR values in a patient taking warfarin is mandatory.
- ▲ For every bleeding episode, many more stroke events are prevented.
- ▲ Nevertheless, anticoagulant therapy is underutilized for stroke prophylaxis, especially in patients with atrial fibrillation.
- ▲ Prescribers must resist using a high loading dose, because not all clotting factors are inhibited by warfarin at the same time.
- ▲ Genetic testing was added to the prescribing information of warfarin last August to improve initial dosing variations and reduce the risk of bleeding, but is currently not covered by most insurance plans.

**Table 1** Pharmacology of Warfarin

• Derivative of 4-hydroxycoumarin residue (carbon substituent at 3 position)
• Water-soluble
• Absorbed within 1 hr, impeded by food
• Highly protein-bound, 99% to albumin
• Actions: <ul style="list-style-type: none"> <li>◦ Decreases availability of vitamin K</li> <li>◦ Decreases production of:           <ul style="list-style-type: none"> <li>Factors II (half-life 50+ hrs), VII (6 hrs), IX (24 hrs), and X (36 hrs); Proteins C (8 hrs) and S (30 hrs)</li> </ul> </li> </ul>
• Metabolized in the liver, excreted renally and hepatically
• Half-life: 36-42 hrs
• Duration of action: 2-5 d
• Response influenced by: genetics, diet, medications, and disease
• Side effects: (most common) bleeding; (less common) skin necrosis, purple toe syndrome, alopecia, dermatitis
• Risk factors: age >65 years; history of GI bleeding; hematocrit <30; diabetes mellitus; previous stroke; myocardial infarction; left ventricular dysfunction; high-intensity anticoagulation (INR >4)
• Contraindications: severe thrombocytopenia, chronic hypertension (>160/90 mm Hg), medication noncompliance, alcoholism, bleeding
• Relative contraindications: nonsteroidal anti-inflammatory drugs without cytoprotection, hazardous activities

GI indicates gastrointestinal; INR, international normalized ratio.

which requires more frequent monitoring.<sup>8</sup> Observations suggest it may be better to use a single tablet strength (eg, 2-mg tablet) and titrate the number of

**Table 2** Herbal and Nutrient Interactions with Warfarin

Potentiate warfarin effects (higher INR)	Inhibiting warfarin effects (lower INR)
<p><i>Drugs</i></p> <p>Acid-neutralizing agents: cimetidine, omeprazole</p> <p>Analgesics: aspirin, nonsteroidal anti-inflammatory drugs, tramadol, acetaminophen</p> <p>Antibiotics: cephalosporins, macrolides, quinolones, doxycyclines, sulphonamides</p> <p>Antidepressants: serotonin reuptake inhibitors, fluoxetine, sertraline</p> <p>Antifungals: fluconazole</p> <p>Statins: lovastatin, simvastatin*</p> <p>Miscellaneous: allopurinol, amiodarone, tamoxifen</p> <p><i>Nutrients</i></p> <p>Alcohol</p> <p>Cranberry products</p> <p>Vitamin E</p> <p><i>Herbals</i></p> <p>Capsicum, cayenne, cloves, danshen, dong auai, garlic, ginkgo biloba, ginseng, mango, papaya, onions, tamarind</p>	<p><i>Drugs</i></p> <p>Antibiotics: dicloxacillin, nafcillin</p> <p>Anti-epileptic: barbiturates, carbamazepine, phenytoin</p> <p>Antipsychotics: clozapine, haloperidol</p> <p>Bile-acid-binding resins</p> <p>Miscellaneous: antacids, sucralfate, ranitidine</p> <p>Steroids, oral contraceptives (estrogen containing)</p> <p><i>Herbals</i></p> <p>Mistletoe, Coenzyme Q10, ginseng, green tea, St. John's wort</p> <p><i>Nutrients</i></p> <p>Vitamins C, K</p>
<p>Note: This is not an exhaustive list.</p> <p>*Data are inconclusive.</p> <p>INR indicates international normalized ratio.</p>	

tablets daily or weekly rather than provide new prescriptions for every INR alteration.<sup>5</sup>

### Pharmacogenetics

Periodically one encounters hereditary resistance, where patients require large doses of warfarin, up to 20 mg daily, to achieve adequate anticoagulant effect. This is possibly due to a decline in affinity of warfarin to receptors in the liver.<sup>4</sup> In contrast, 10% of patients require smaller-than-usual doses and have greater bleeding tendencies; they inherit variant alleles of the cytochrome (CY) P450 system that cause failure of conversion of S warfarin to metabolites.<sup>4</sup> Pharmacodynamic effects of warfarin are explained by genetic polymorphisms in the 2C9 isoform of CYP450 (CYP2C9) and vitamin K epoxide reductase (VKORC1); combined with factors such as age, sex, height, weight, and smoking status, they account for more than half the variance in warfarin dose.

Pharmacogenetic tests to guide clinical utility can help predict dosing of warfarin,<sup>9,10</sup> but are not currently used. Initial variations in the INR with warfarin use

were more strongly linked to the VKORC1 haplotype than the CYP2C9 genotype.<sup>11</sup> However, in a randomized controlled study, pharmacogenetic-guided and standard dosing did not differ for out-of-range INRs in patients initiated with warfarin therapy.<sup>12</sup>

In August 2007, the FDA revised the prescribing information for warfarin, “to explain that people’s genetic makeup may influence how they respond to the drug.”<sup>10</sup> The FDA noted that the variability in a patient’s response to the drug depends on genetic variations, hence the need for genetic testing before the initiation of warfarin therapy. This labeling change, according to the FDA, would allow physicians to ensure that the initial dosing is not too large and therefore does not increase the risk for bleeding.<sup>10</sup> Despite the FDA ruling, most health plans still do not cover genetic testing for this purpose. A recent prospective study provides further evidence in favor of genetic testing.<sup>9,13</sup>

### Indications and Contraindications

A MEDLINE literature review indicates that physicians’ fears of bleeding from anticoagulants are

unfounded<sup>14</sup>; anticoagulant therapy is underused for stroke prophylaxis, especially in patients with atrial fibrillation (AF). Long-term warfarin use for most causes of AF is effective in significantly decreasing stroke risk, and has a low risk of intracranial bleeding.<sup>7,15</sup> Between 1995 and 2002, trends in anticoagulation for AF have been on the rise, although many patients at risk for thromboembolic events were not anticoagulated.<sup>15,16</sup>

Warfarin (or heparin) is indicated as prophylaxis of deep-vein thrombosis in settings of restricted mobility or high-risk situations—the perioperative period (in particular orthopedic knee and hip surgery), heart failure, a history of cerebrovascular event (nonhemorrhagic, unrelated to AF), and any other hypercoagulable state. In such high-risk situations, INR is targeted to the 2 to 3 range. The presence of a mechanical prosthetic valve, depending on the type, location (mitral or aortic), and associated risk factors, will require long-term anticoagulation, with a target INR range of 2 to 3.5; with bioprosthetic valves, the presence of other risk factors dictates long-term use.<sup>4</sup>

The disadvantages of warfarin therapy include cost of testing, inconvenience from regular INR monitoring, and most important, bleeding complications. Unlike bleeding into the skin or from the gums that may be without consequence, intracranial and gastrointestinal (GI) bleeding can be life-threatening and is a basis for physician reluctance to prescribe long-term anticoagulants.<sup>14,16</sup>

Risk factors and contraindications are not universally accepted and are well-reviewed in a systematic literature search.<sup>14</sup> Predisposition to falls and the presence of dementia are not contraindications; in a study of a long-term care resident with dementia and AF predisposed to falls, most physicians surveyed believed anticoagulation was contraindicated.<sup>14,16</sup> Patients with mild-to-moderate dementia can use anticoagulants if supervised.

Contraindications include hazardous or sports activities associated with the risk of head trauma, noncompliance and refusal to follow regular monitoring, and excessive alcohol consumption. Current bleeding is a contraindication, but a healed peptic ulcer is not.

Control of blood pressure above 160/90 mm Hg is suggested before initiating warfarin therapy.<sup>14,17</sup> Past GI bleeding is a risk factor for bleeding with warfarin.<sup>17</sup> Concomitant use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 inhibitors incur similar increased risk of hospitalization for upper-GI hemorrhage.<sup>18</sup> Increasing age and intensity of anticoagulation (INR >4) are risks. Patient (caregiver) and provider preferences may influ-

ence decisions on anticoagulation.<sup>14,16</sup> Older adults may not need closer monitoring than younger adults.<sup>19</sup>

### Drug–Nutrient Interactions

Warfarin use is complicated by interactions with drugs, nutrients, and herbals, which potentiate or inhibit the anticoagulant effect. The mechanisms for interaction vary considerably (Table 2). Cephalosporins inhibit cyclic interconversion of vitamin K<sub>4</sub>; thyroxine enhances metabolism of clotting factors; and the mechanism involving clofibrate is unclear. Aspirin and NSAIDs inhibit platelet function, increase the prothrombin time, and augment the pharmacodynamic effect of warfarin.<sup>4,18</sup> Sulfa and several antibiotics deplete the gut of bacterial flora and worsen vitamin K status.<sup>20</sup> Amiodarone causes dose- and concentration-dependent inhibition of warfarin elimination.<sup>21</sup> Alcohol interactions are variable; acute alcoholism may inhibit warfarin metabolism, increasing

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the INR; long-term use may induce liver enzymes and lower the INR; further liver disease increases sensitivity to warfarin.<sup>5</sup>

Adding antiplatelet agents (clopidogrel and acetylsalicylic acid) to warfarin increases GI-bleeding risk beyond the risk with each drug alone.<sup>22</sup> Coadministration of warfarin and aspirin increases bleeding risk, but this combination increases the benefits for patients with acute coronary syndrome, a coronary stent, or a mechanical valve.<sup>23</sup>

Acetaminophen, perceived as the safest analgesic in the elderly, is an underrecognized cause of anticoagulant instability<sup>24</sup>; it slows the degradation of warfarin through the CYP450 system, increasing the active (free) fraction.

Use of complementary and alternative medicine with warfarin risks a supratherapeutic INR and bleeding events<sup>25</sup>; cranberry juice has low-level interaction potential<sup>26</sup>; oral corticosteroids can have a significant interaction.<sup>27</sup>

The effect of statins is inconsistent, requiring further



**Table 3** A Practical Approach to Warfarin Use**The basics**

- Focused history, including cognition, activities, alcoholism, comorbidity
- Laboratory: routine, including baseline INR, hemoglobin, platelet count, hepatic, renal, and thyroid function status
- Medication reconciliation: review prescribed, herbals, and over the counter
- Review typical dietary preferences of the individual
- Counsel patient on need to avoid marked variations in diet (particularly vitamin K-containing foods) and to review use of herbals with physician

**Warfarin initiation, maintenance**

- Starting dose  $\leq 5$  mg/d in elderly; avoid larger doses
- Maintenance, typically 2-5 mg/d; adjust to target INR
- May increase dose if overweight and warfarin resistance exists
- May lower dose in warfarin sensitivity, concomitant drugs, comorbidity
- Monitor INR daily until at target, then monthly
- Monitor INR more often in acute illness, diet/medication changes

**Managing a high INR**

- INR  $< 5$  and no bleeding, withhold 1-2 doses, revise subsequent dosing
- INR 5-9, with greater risk of bleeding, do as above; consider oral vitamin K, 1-5 mg
- If there is bleeding, with requirement to reverse anticoagulation (high INR), withhold warfarin, consider IV vitamin K (5-10 mg slow IV infusion, 30 min), fresh frozen plasma, and/or prothrombin complex concentrate. Therapy is individualized to clinical situation, risks
- Contact health provider to consider hospitalization
- Revise medication regimen; is warfarin to be continued in the individual?

**Perioperative**

- Withhold warfarin 4-5 d presurgery, but not necessary for minor procedures (consider provider and patient preferences)
- High-risk perioperative states (eg, mechanical prosthetic heart valves), may substitute warfarin using “bridge” therapy (unfractionated/low-molecular-weight heparin)
- Ensure INR is at acceptable range presurgery

INR indicates international normalized ratio; IV, intravenous.  
Adapted from Reference 14.

evaluation.<sup>28</sup> Clinically significant alterations in coagulation have not been observed with the influenza, pneumococcal, or tetanus vaccines.<sup>29</sup>

**Patient Education, Monitoring**

Every patient (or caregiver if the patient is incapacitated) should be counseled on the proper use of warfarin. Instructions should include an understanding of

the interactions with warfarin. This can be simplified by the “3 Ds” mnemonic—Diet, Drug, Disease.<sup>30</sup> Patients should be instructed to review any drug changes with their primary physician, including herbal and over-the-counter medications. Most dietary supplements affect the INR. Change in health status (even just fever) and hospitalization calls for frequent monitoring; any newly introduced medications (eg, antibiotics and analgesics) will cause changes in the INR. In addition, illness such as liver disease, malabsorption, or thyroid dysfunction cause alterations in requirement of warfarin and INR results.<sup>30</sup> The physician should be contacted for any signs of bleeding or before switching from a branded to a generic product, or vice versa. Patients should also minimize hazardous activities prone to injury.

It is most important not to tell patients to avoid vitamin K-rich foods (spinach, greens, broccoli, and lettuce) but rather to keep dietary content consistent, avoiding indulgence. When the INR is not at target, management is focused on the INR and potential bleeding. The severity and site of bleeding may demand prompt attention. For high INR, decreasing or skipping 1 or 2 doses will usually suffice and the regimen is reevaluated; increasing the dose may be warranted for subtherapeutic INR. When vitamin K is required to counter warfarin effects, oral formulations are more predictable and effective than subcutaneous<sup>31</sup>; the intravenous (IV) slow infusion is used in the presence of bleeding relating to high INR. It is also necessary to search for the reason the INR is not at target, such as a compliance issue, an illness, or a change in diet or medication.<sup>4,6</sup> **Table 3** outlines a practical approach to the use of warfarin.

**The Perioperative Period**

Most patients can undergo dental procedures, cataract surgery, and endoscopy without biopsy, avoiding alterations in the warfarin regimen, although decisions should be individualized.<sup>32</sup> For invasive or major procedures, warfarin must be withheld, and a decision must be made on the requirement for “bridging” therapy with IV or subcutaneous unfractionated heparin or low-molecular-weight heparin.<sup>4,32</sup> The decision incorporates the indications for anticoagulation, risks and benefits of withholding warfarin, and the surgeon’s preferences as well.

In high-risk situations, such as AF in valvular heart disease, previous stroke, or a mechanical prosthetic valve, it is prudent to stop warfarin 4 to 5 days before the procedure and use bridge therapy.<sup>4</sup> Bridging antico-

agulation may be considered for patients at high risk for thromboembolism.<sup>33</sup>

## Conclusions

Although pharmacogenetic testing has the potential to allow for safer prescribing of warfarin, the FDA has not provided clear guidelines, which would encourage coverage by health plans. Patient self-testing to monitor the INR or self-management of anticoagulation instead of monitoring in the clinic has the potential to ease the burden on patients, improve control, and cut the costs associated with long-term oral anticoagulation.

The 2008 National Patient Safety Goals promote specific improvements in patient safety, such as improving the safety of using medications and reducing the likelihood of harm associated with the use of anticoagulant therapy, including warfarin, by providing healthcare organizations with proved solutions to patient safety problems; these goals apply to more than 15,000 Joint Commission-accredited and certified healthcare organizations and programs. By consistently meeting these goals, healthcare organizations can substantially improve patient safety and quality of care and reduce costs. ■

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## Stakeholder Perspective

### Benefits of Genetic Testing in Warfarin Therapy

**PAYORS:** Personalized medicine provides powerful new tools that can help physicians prescribe medications with greater precision. Using advanced genetic and biomarker testing, physicians can more easily predict whether a drug or dosage is likely to be effective—or potentially toxic—for an individual patient.

For many drugs, such as warfarin, product labeling already includes information about the possible impact of genetic variations on drug response, but this information is not yet generally used in clinical practice. Widespread use of genetic testing will depend on several factors, including evidence of clinical and economic benefits, easy access to genetic testing, and the integration of this new type of diagnostic testing into health benefits.

For drugs like warfarin, determining the appropriate dose early in treatment is crucial. If patients reach therapeutic levels more quickly, hospitalizations due to serious adverse events are less likely. In a recent analysis of patients who were new to warfarin therapy, Medco researchers found that patients who required 2 or more dose adjustments had a significantly higher risk of hospitalization for hemorrhage or thrombosis (30.7%), compared with patients who required 1 or fewer dose adjustments (19.6%). Testing for genetic differences in warfarin metabolism could help clinicians stabilize warfarin doses early in treatment, thereby reducing the costs associated with hospitalization—the most expensive component of the healthcare system.

A recent study demonstrates that genotype testing can have a positive impact on warfarin therapy in controlled clinical settings.<sup>1</sup> Patients in a genotype-adjusted treatment group achieved therapeutic levels more quickly, spent more time in the therapeutic range, and had fewer minor bleeding events compared with patients in a control group.

Many clinicians agree that pharmacogenomic testing is theoretically sound, but they are not yet convinced that its value has been proved in practice. Medco is working on closing the gap between theory and practice by collaborating with the Mayo Clinic on a study to assess the clinical value of genetic testing in warfarin therapy. Patients who are new to warfarin treatment are offered genetic testing to determine

how sensitive they may be to the drug's effects on blood clotting. This information is provided to the physician, who can use it to adjust the dose. The objective is to see whether early dose adjustments based on genetic information will result in a lower incidence of complications and hospitalizations. This study will provide the first broad evaluation of personalized medicine in typical community practice settings.

If clinical research demonstrates that genetic testing can reduce the risk of serious adverse events in patients using warfarin, the potential savings could be substantial in human and financial terms. The American Enterprise Institute-Brookings Joint Center predicts that using genetic information to prescribe warfarin could save an estimated \$1.1 billion in healthcare spending each year, while preventing about 17,000 strokes and 85,000 serious bleeding incidents.<sup>2</sup>

For health plan sponsors, personalized medicine offers the potential to bring greater precision to medication prescribing. Coverage programs could be more specifically designed based on the genetic profile of the individual patient. For example, medications that work through certain genotypes or biomarkers could be limited to patients who exhibit those targets.

Personalized medicine can help ensure that patients receive the correct dose of the right drug at the earliest possible point in their treatment. Precise, individualized prescribing offers significant potential for improving health outcomes and patient safety, while reducing the overall costs of care.

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